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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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SUITE 2400
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EXAMINER	
HA, JULIE	
ART UNIT	**PAPER NUMBER**
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/784,721	MUIR ET AL.	
	Examiner	Art Unit	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-68* is/are pending in the application.

4a) Of the above claim(s) *52-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51 and 63-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment filed on September 01, 2006 is acknowledged. Claims 51-68 are pending in this application.

Election/Restrictions

1. Applicant's election without traverse of SEQ ID NO: 9 as the FRET enzyme substrate species in the reply filed on September 01, 2006 is acknowledged. Claims 51-66 and 68 read on the elected species and will be examined for examination purposes. Claim 67 is withdrawn from further examination. Claims 51-66 and 68 are pending in this application.

2. Search was performed for SEQ ID NO: 9 and 10. These SEQ ID NOs were deemed to be free of prior art. Search was then extended as stated in MPEP § 803.02: "Should the examiner determine that the elected species is allowable, the examination of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all nonelected species." For Markush type claim 51, prior art was found that anticipated claim 51. Since prior art reads on claims 51, and 63-66, those claims have been rejected and claims 52-62 are hereby withdrawn as corresponding to nonelected species. Claims 67 and 68 are free of the prior art. Claims 51 and 63-68 have been examined on the merits in this application.

Objection-Specification

3. The disclosure is objected to because of the following informalities: On paragraphs 0047, 0075, 0081, 0087, 0095, 0097, and 0116, the character "N" in "N- and C-termini" is missing.

Appropriate correction is required.

Rejection-35 U.S.C. 112, 2nd

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 51 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. In claim 51 the word "proximity-sensor" and " at a distance which is" is unclear. According to a dictionary, the work proximity means "nearness in place, time, order, occurrence, or relation". Therefore, this word can mean near something, near some time, or in "queue" of something. Thus it is indefinite. The word "at a distance" is indefinite since this can be very far distance or close distance. According to a dictionary, the word "distance" means" the extent of amount of space between two things, points, lines, etc; the state or fact of being apart in space, as of one thing from another, remoteness; an expanse or area; an amount of progress; remoteness or difference in any respect; absence of warmth, reserve". With so many meanings that can be applied to the word "distance", thus, it is indefinite.

Claims Rejection-35 USC 112, 1st

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 51, 63-68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the

claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a composition comprising a functional peptide substrate having a first detectable proximity-sensor peptide incorporated into a first position of said substrate and a second detectable proximity-sensor peptide incorporated into a second position of said substrate wherein said first and second detectable proximity-sensor peptides comprise a FRET pair. The generic statements functional peptide substrate, fluorescent amino acid derivative, and FRET pair do not provide ample written description for the compounds since the claims do not describe a single structural feature. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention.

As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claims 51, 63 and 66 are broad generics with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of peptide or a peptide-like molecule, any type of post-translational modifications, and any FRET pair. It must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a

correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives. The specification is void of organic molecules that functions as a peptide-like molecule that qualify for the functional characteristics claimed as a peptide or a peptide-like molecule or substrates or modulators or fluorescent compounds. The specification is limited to the peptide or peptide-like molecules that belong to the same class of peptide substrate, Crk-II. The specifications do not describe peptide substrate beyond said tyrosine kinase substrates. Additionally, the specifications do not describe post-translational modification beyond said phosphorylation and desphosphorylation. Further, the specifications do not describe enzymes and modulators beyond said tyrosine kinase and agonists or antagonists of c-Abl activity. Furthermore, the specifications do not describe Fluorescence Resonance Energy Transfer (FRET) beyond EDAN, IAEDANS, DABCYL, BODIPY fluorescein, beta-phycoerythrin, CY5, pyrene and coumarin. For example, the specifications do not describe any other compounds, such as organic compounds, that can act as donor and acceptor fluorophores.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will

hopefully ameliorate"). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Rejection-35 U.S.C. § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 51 and 63-66 rejected under 35 U.S.C. 102(b) as being anticipated by Garman AJ (US Patent # 6291201).

The instant claims are drawn to a composition comprising a functional peptide substrate having a first and second detectable proximity-sensor peptides of said semi-synthetic multiple labeled polypeptide comprise a FRET pair, wherein, FRET pair is fluorescein and tetramethylrhodamine.

Garman AJ teaches a method for the preparation of a fluorescence resonance energy transfer (FRET) substrate having donor and acceptor species on opposite sides of a proteolytic cleavage site (see abstract). The reference further teaches that the fluorophores is preferably attached after synthesis of the polypeptide chain of the protease substrate. The visible light fluorophores include fluorescein, Lucifer Yellow, acridine Orange, rhodamine and its derivatives, for example tetramethylrhodamine and

Texas Red, and fluorescent chelates or cryptates of Europium (see column 4, lines 21-32). Furthermore, Example 1 teaches the preparation of the peptide synthesis and preparation of fluorescein and tetramethylrhodamine to the synthesized peptide (see column 5, lines 29-58). When the methods of US Patent # 6291201 is practiced, one would necessarily lead to the composition of instant application, therefore, this reads on claims 51, 63-66.

11. Claims 51, 63-64, and 66 are rejected under 35 U.S.C. 102(b) as being anticipated by Gulnik et al (FEBS Letters, 1997, 413: 379-384).

The instant claims are drawn to a composition comprising a functional peptide substrate having a first and second detectable proximity-sensor peptide comprising a FRET pair, wherein the FRET pair consists of EDANS and DABCYL.

However, Gulnik et al teach a number of fluorogenic substrates having EDANS and DABCYL donor-acceptor pair (see page 380, 2.2. Synthesis). The fluorescent signal in uncleaved substrate is quenched due to resonance energy transfer between the fluorophore and quencher groups. This reads on claims 51, 63-64 and 66. The increase in fluorescence during substrate cleavage can be continuously monitored using fluorescence spectroscopy (see page 379, right column, second paragraph). Furthermore, the reference teaches that to facilitate the search for specific inhibitors of cathepsin D and to facilitate studies of its enzymology, it is necessary to have a sensitive and continuous assay for enzyme activity (see page 379, right column, first paragraph). The differences between the reference and the instant claims are that the reference does not teach other fluorophores.

12. Claims 51, 63-64 and 66 are rejected under 35 U.S.C. 102(b) as being anticipated by Jones et al (Analytical Biochemistry, 1997, 251: 144-152).

The instant claims are drawn to a composition comprising a functional peptide substrate having a first and second detectable proximity-sensor peptide comprising a FRET pair, wherein the FRET pair consists of BODIPY fluorescein and BODIPY FL fluorescein.

However, Jones et al teach Quenched BODIPY Dye-labeled Casein substrates for the assay of protease activity by direct fluorescence measurement. The reference teaches that BODIPY dye-labeled casein protease assays to be simple and precise and to have greater sensitivity and broader dynamic range of detection than the fluorescein thiocarbamoyl assay (see abstract). Furthermore, the fluorescence proteins conjugated at multiple sites with BODIPY dyes is efficiently quenched with no shift in excitation spectrum, even at relatively low degrees of labeling. BODIPY dyes can be prepared with a wide range of excitation and emission wavelengths, thus, preparation of quenched BODIPY conjugates with spectral characteristic similar to those of fluorescein, with green fluorescence emission and to Texas Red dye, with red fluorescence emission is possible (see page 145, left column, third paragraph continuing onto right column). Additionally, the reference teaches that casein labeled with multiple BODIPY dyes are general protease substrates useful for the sensitive detection of a wide variety of proteolytic enzymes. These fluorogenic substrates provide a simple assay that is easily automated with good sensitivity and a broad responsive

range for detection of a variety of proteases (see pages 151-152, last paragraph). This reads on claims 63-64 and 66.

Rejection-35 U.S.C. § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 51 and 63-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gulnik et al (FEBS Letters 1997, 413: 379-384) in view of Garman AJ (US Patent # 6291201) and in further view of and in further view of Lakowicz JR (Principles of Fluorescence Spectroscopy, second edition, 1999).

The instant claims are drawn to a composition comprising a functional peptide substrate having a first and second detectable proximity-sensor peptides comprises a FRET pair, wherein the FRET pair consists of fluorescein and tetramethylrhodamine, IAEDANS and fluorescein, EDANS and DABCYL, BODIPY fluorescein and BODIPY FL fluorescein, *-phycoerythrin and CY5, and pyrene and coumarin, and substrate further comprising a modulator of said enzyme, wherein said modulator of said enzyme inhibits and activates said enzyme activity.

Garman AJ teaches a FRET substrate having donor and acceptor species on opposite sides of a proteolytic cleavage site, wherein the FRET pair are fluorescein and tetramethylrhodamine (see paragraph 9 above). Furthermore, the reference teaches that after synthesis of the polypeptide substrate, a donor or acceptor is attached via the side chain of an amino acid comprised in the polypeptide. This allows a wide range of donor and acceptor pairs, many of which are commercially available, to be attached to the peptide structure. Accordingly, desirable donor and acceptor combinations may be readily selected (see column 1, lines 60-67). The reference further teaches a novel FRET substrates and their use in assays to identify modulators of protease activity (see abstract). This reads on claims 51, 58-60, and 63-64. The differences between the

reference and the instant claims are that the reference teaches only fluorescein and tetramethylrhodamine donor-acceptor pair.

However, Lakowicz JR teaches that FRET is transfer of the excited-state energy from the initially excited donor (D) to an acceptor (A). The donor molecules typically emit at shorter wavelengths which overlap with the absorption spectrum of the acceptor (see Chapter 13, pages 367-394). Furthermore, the reference teaches that the most common application of RET is to measure the distances between two sites on a macromolecule. Typically, a protein is covalently labeled with a donor and an acceptor. The donor is often a tryptophan residue, but extrinsic donors are also used (see page 367, second paragraph). The reference teaches measuring the association of catalytic and regulatory subunits of the cAMP-dependent protein kinase. The subunits were labeled with fluorescein (carboxyfluorescein succinimidyl ester) and rhodamine (Texas Red sulfonyl chloride) derivatives. Binding will bring donor and acceptor within the Forster distance, resulting in energy transfer. Additionally, the dissociation constant of cAMP from the protein can be measured using the RET data (see pages 378-379). Additionally, the reference teaches many possible fluorophores that can be used as donors and acceptors (see Chapters 3 and 13, pages 63-92 and 367-394). In chapter 3, the reference teaches numerous fluorophores are available for covalent and noncovalent labeling of proteins. The covalent probes can have a variety of reactive groups, for coupling with amine, sulfhydryl, or histidine side chains with proteins. Some of the more widely used probes are Dansyl chloride, TRITC, FITC, Acrylodan, 5-IAF,

NBD-Cl. Fluoresceins and rhodamines are also widely used as extrinsic labels (see pages 66-69).

Therefore, it would have been obvious to the ordinary skilled in the art to choose any fluorophores taught by Lakowicz to label any peptide, substrate, proteins to measure the dissociation or association of these compounds since FRET is transfer of the excited-state energy from the initially excited donor (D) to an acceptor (A). The donor molecules typically emit at shorter wavelengths which overlap with the absorption spectrum of the acceptor. It is known to the ordinary skilled in the art that the donor and acceptor fluorophores are positioned either side of the bond to be cleaved and are sufficiently close such that a large proportion of the fluorescence of the donor fluorophores of the fluorescence is quenched by radiation-less energy transfer to the acceptor. Cleavage causes a large increase in separation of the donor and acceptor which is made manifest by an increase in fluorescence (see Garman Patent, column 1, lines 11-22). Garman Patent teaches that the methods may be applied to any convenient substrate for proteolytic cleavage, provided that the recognition site(s) and site for proteolytic cleavage are present (see column 3, lines 51-56).

There is a reasonable expectation of success since those skilled in the art knows that the donor and acceptor pairs are commercially available (see Garman Patent, column 1, lines 64-66) and using the teachings of Lakowicz, can determine which donor-acceptor pair is best for the experiments. Additionally, the FRET pair works on many enzyme activity measurements measuring fluorescence measurement on substrate cleavage with FRET attachments (see Garman).

Conclusion

17. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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11/3/09
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PRIMARY EXAMINER